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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/210,995	12/15/98	LOOSMORE S	1038-844MIS:

EXAMINER	
HINES, J	
ART UNIT	**PAPER NUMBER**
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AIR MAIL

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No. 09/210,995	Applicant(s) Loosmore et al.
	Examiner Ja-Na Hines	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Dec 15, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because Michel Klein did not date the declaration.

Specification

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The claims are indefinite because of the use of acronyms like PRP-T. The acronym must be spelled out when used for the first time in a chain of claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-5 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Barenkamp et al. (Mol. Microbio. 1996). Barenkamp et al., teaches the identification of a second family of high molecular weight adhesion protein expressed by non-typeable *Haemophilus influenzae*. Barenkamp et al. (Mol. Microbio. 1996), identified two closely related adhesion proteins designated High Molecular Weight 1 and 2 (HMW1 and HMW2) (abstract). These proteins have high immunogenic character during the course of infection in a child with acute non-typeable *Haemophilus influenzae* otitis media and its immunogenicity and role as an adhesion protein suggest it potential role as a vaccine candidate (page: 1220 para. 4). The authors state "...Vaccines based upon adhesins critical to non-typeable *H. influenzae* colonization process would also be very attractive candidates for prevention of disease. If combined with representative HMW1/HMW2-like proteins and a Haemophilus Influenzae Adhesin (Hia) -like

proteins a vaccine formulation could be envisioned that would be protective against most or all non-typeable *H. influenzae* diseases (abstract and pages:1220-1221 para. 4-1).

Thus Barenkamp et al. (Mol. Microbio. 1996), teaches an immunogenic or vaccine composition which would be protective against disease caused by non-typeable *H. influenzae* comprising at least one adhesin antigen which is a high molecular weight protein, HMW1 or 2 from non typeable *H. influenzae,* thus teaches the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barenkamp et al., (WO 97/36,914) in view of Loosmore et al. Barenkamp et al.(WO 97/36,914), teaches high molecular weight surface proteins of non-typeable Haemophilus. The high molecular weight surface proteins of non-typeable *Haemophilus influenzae* which exhibits immunogenic properties and genes encoding for two immunodominant high molecular weight proteins, HMW1, HMW2, HMW3 and HMW4. HMW3 and HMW4 show considerable homology to HMW1 and HMW2 thus HMW3 and HMW4 are also likely to function as adhesins (page 18 lines 14-17). The

invention also teaches an immunogenic composition comprising the novel high molecular weight protein or synthetic peptide along with a pharmaceutically acceptable carrier for in vivo administration to a host (page 6 lines 20-27). The immunogenic composition may also comprise at least one other immunogenic or immunostimulating material and at least one adjuvant (page 7 lines 1-5). Barenkamp et al.(WO 97/36,914), also teaches a list of suitable adjuvants including aluminum phosphate and aluminum hydroxide (page 7 lines 6-17). The high molecular weight proteins can be produced recombinantly (page 10 lines 21-25) and that HMW1 and HMW2 have apparent molecular weights of 125 and 120 kDa respectively produced from non-typeable *Haemophilus* (page 15 lines 21-24) and HMW3 and HMW4 have apparent molecular weights of 125 and 123 kDa from non-typeable *Haemophilus*. One example illustrates the use of HMW antigens composed in an immunogenic composition containing 40ug of HMW protein and Freund's adjuvant, the mixture was administered to a host (chinchillas) infected with Haemophilus influenzae causing otitis media (pages 47-48 lines 29-33). Barenkamp et al.(WO 97/36,914), teaches complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen and others (page 24-25 lines 7-10). Finally, Barenkamp et al's.(WO 97/36,914), data teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine (page 49 lines 15-19). Barenkamp et al.(WO

97/36,914), however does not teach the use of a heat shock protein in an immunogenic composition.

Loosmore et al., teaches an analog of *Haemophilus* Hin47 with reduced protease activity. The Hin47 protein is conserved among strains of *Haemophilus influenzae* and is reported to have utility in vaccination against disease caused by *H. influenzae* or other bacterial pathogens that produce Hin47 or proteins capable of rasing antibodies specifically reactive with Hin47 (col. 2 lines 16-21). Loosmore et al., teaches that it would be advantageous to provide analogs of Hin47 that are substantially reduced in proteolytic activity for use as an antigen or to be included in other immunogenic preparations (col. 2 lines 29-34). The isolated and purified analog has decreased protease activity which is less about than 10% of natural Hin47, yet still retains substantially the same immunogenic properties, where at least one amino acid contributing to protease activity may be deleted or replaced by a different amino acid to produce reduced activity (col. 2 lines 44-54). "The at least one deleted or replaced amino acid may be selected from amino acids 195-201 of Hin47, and specifically may be Serine-197, which may be deleted or replaced by alanine. In addition, the at least one deleted or replaced amino acid may be His-91 and may be deleted or replaced by alanine or lysine or arginine. Further, the at least one deleted or replaced amino acid may be Asp-121 and may be deleted or replaced by alanine or glutamic acid" (col. 2 lines 56-64). An immunogenic composition comprising an immuno-effective amount of Hin47 analog may be formulated as a vaccine for *in vivo* administration to a host, including a human to confer protection against diseases caused by a bacterial pathogen, including

Haemophilus influenzae (col. 3 lines 47-59). The immunogenic composition may further comprise at least one other immunogenic or immunostimulating material such as an adjuvant, and may be contained within a live vector such as a pox virus, salmonella, poliovirus, adenovirus, vaccinia or BCG (col. 3-4 lines 60-2). The analogs may be used as carrier proteins to make conjugate vaccines against antigenic determinants unrelated to Hin 47" (col. 7 lines 15-18) including pathogenic bacteria (col. 7 lines 40-51). The Hin47 analogs my be prepared with pharmaceutically acceptable carriers, adjuvants such as aluminum hydroxide or phosphate and should be administered in dosage ranges readily determinable by one skilled in the art (col. 8-9 lines 33-6).

Therefore it would have been obvious at the time of applicant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, where one is a high molecular weight adhesin protein, HMW1 or HMW2, since Barenkamp et al.(WO 97/36,914), teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine and the other component is an analog of Hin47 which is a non-proteolytic heat shock protein with reduced protease activity from *Haemophilus influenzae* as taught by Loosmore et al. One would expect a reasonable level of success by combining known adhesin proteins and known Hin47 analogs in a multi-component immunogenic composition since Barenkamp et al.(WO 97/36,914), and Loosmore teach the use the these antigens in immunogenic compositions. Further, both Barenkamp et al.(WO 97/36,914), and Loosmore et

al., teach the use of adjuvants, and the addition of other additional antigenic components and methods for immunizing a host against disease caused by an infection with *H. influenzae* comprising administration of the composition.

Prior Art

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Arminjon et al., teaches a vaccine composition containing one or more antigens comprising high molecular weight capsular polysaccharides of type b *Haemophilus influenzae* coupled to the tetanus toxoid and an aluminum-based adjuvant. Barenkamp et al (US Patent 5,549,897) teaches high molecular weight surface proteins of non-typeable *Haemophilus*. Barenkamp (Infection and Immunology 1996) teach that the high molecular weight adhesion proteins are potentially important protective antigens which represent one component of a multi-component non-typeable *Haemophilus* vaccine and that administration with *Bordetella pertussis* may provide that highest level of protection against disease. Brinton teaches that it is reasonable to expect that pilin, chaperone, anchors, minor tip and large minor tip adhesin proteins of *H. influenzae* can be produced to form multivalent vaccines. Hauser et al., teaches combined hepatitis B surface antigen and other antigens. Erich et al., teaches novel polysaccharides and novel macromolecular conjugates of the polysaccharide. Massimo et al., teaches glyoproteinic conjugates having trivalent immunogenic activity.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

April 12, 1999

James C. Housel 4/12/99

JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER